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Official Title of the study:	**Comparative randomized crossover study of tolerance and pharmacokinetics of Primapur, solution for subcutaneous injection 300 IU (IVFarma, LLC, Russia), and Gonal-f®, solution for subcutaneous injection 300 IU (Merck Serono S.p.A., Italy), given subcutaneously as a single dose to healthy volunteers**
Ethics approval and consent to participate:	**The study protocol and informed consent were approved by the Russian Ministry of Health (RCT 547 dated 30.09.15).**
Unique Protocol ID:	**FSG-01-01**
NCT number:	**NCT03857230. Date of registration: February, 26, 2019, retrospectively registered.**
General Manager/IVFarma LLC **Mikhail Polzikov (PhD)**	**26.02.2019**

	STUDY EXECUTIVE SUMMARY		
Study Sponsor:	iVFarma, LLC, Russia		
Study name:	Comparative randomized crossover study of tolerance and pharmacokinetics of Primapur, solution for subcutaneous injection 300 IU (iVFarma, LLC, Russia), and Gonal-f®, solution for subcutaneous injection 300 IU (Merck Serono S.p.A., Italy), given subcutaneously as a single dose to healthy volunteers		
Study type	Phase I		
Protocol No.:	No. FSG-01-01	**Version:**	1.0 of June 26, 2015
Aims and objectives of the study:	Aim: to study the safety and tolerability, as well as to compare the pharmacokinetic characteristics of Primapur (iVFarma, LLC, Russia) and Gonal-f® (Merck Serono S.p.A., Italy) given subcutaneously as a single 300 IU dose to healthy volunteers Objectives of the study: 1. To evaluate the frequency and severity of adverse events (AE) following a single 300 IU subcutaneous injection of Primapur (iVFarma, LLC, Russia) and Gonal-f® (Merck Serono S.p.A., Italy) to healthy volunteers. 2. To determine the AUC_{0-t} value of Primapur (iVFarma, LLC, Russia) following a single 300 IU subcutaneous injection to healthy volunteers. 3. To determine the $T_{½}$ value of Primapur (iVFarma, LLC, Russia) following a single 300 IU subcutaneous injection to healthy volunteers. 4. To determine the C_{max} value of Primapur (iVFarma, LLC, Russia) following a single 300 IU subcutaneous injection to healthy volunteers. 5. To determine the T_{max} value of Primapur (iVFarma, LLC, Russia) following a single 300 IU subcutaneous injection to healthy volunteers. 6. To compare the obtained pharmacokinetic characteristics of Primapur (iVFarma, LLC, Russia) and Gonal-f® (Merck Serono S.p.A., Italy)		
Study drug:	**Drug product name:**	Primapur	
	Active substance:	Follitropin alfa	

	Presentation:	Solution for subcutaneous injection 33 μg/0.75 mL.
	Manufacturer:	Medgamal Branch of the N. F. Gamaleya Federal Research Center for Epidemiology & Microbiology of the Ministry of Healthcare of the Russian Federation
	Dose	22 μg (300 IU) of the solution for subcutaneous injection, follitropin alfa (0.5 mL)
	Administration:	Injected subcutaneously once
Comparator drug:	**Drug product name:**	Gonal-f®
	Active substance:	Follitropin alfa
	Presentation:	Solution for subcutaneous injection 22 μg/0.5 mL.
	Manufacturer:	Merck Serono S.p.A., Italy
	Dose	1 pre-filled syringe with follitropin alfa 22 μL (300 IU)
	Administration:	Injected subcutaneously once
Study design:	A prospective randomized cross-over two-stage clinical study with the use of the active comparator drug in healthy volunteers.	
Study population	It is planned to include 24 healthy female volunteers aged 18 to 40 years inclusively, who have been enrolled according to the inclusion and non-inclusion criteria. 4 back-ups are planned to be enrolled in the study to replace the volunteers excluded before the study completion.	
Wash-out period between the treatments	10 days	
Blood samples collection for testing	Blood samples to study the pharmacokinetics are to be collected via a venous catheter, which is placed by means of vein puncture before any injection of r-hFSH. Blood sampling will be carried out at certain time points according to the specified scheme: - 20 minutes (20 minutes before the drug injection), 0 hours (immediately prior to injection), and 1, 2, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, 120, 168, and 192 hours after each injection of	

	the drug product. It corresponds to 34 blood samples per one volunteer during the whole study (2 periods) and to a maximal total number of 816 samples within the study (provided 24 volunteers are randomized).
Examination of the volunteers at screening	Obtaining of the informed consent, primary physical check-up, collection of anthropometric data (body weight, growth, BMI calculation), and medical history (including medicinal products); recording of 12-lead ECG; assessment of vital signs (BP, pulse, body temperature); examination by a gynecologist, USI of pelvic organs, X-ray, urine analysis; complete blood count; blood biochemistry (creatinine, glucose, bilirubin, AST, ALT, AP, free T3, free T4); coagulogram; blood analysis for HIV, HbsAg, HCV, RW; urine analysis for drugs and narcotic substances abuse; pregnancy test (for women of child-bearing potential), respiratory alcohol level test. After the screening period, the volunteers will have to discontinue the combined oral contraceptives (COC) for 1 week, and after that they will receive Yarina® (Bayer Pharma AG, Germany) 1 tablet daily (in the evening after meal) to suppress endogenous production of gonadotropins. Yarina® is prescribed for 6 weeks (42 days in total). 1 day before injection of one of the study drugs (day 20 of Yarina® administration – day 27 of the study – visit No. 1), blood samples are taken in the volunteers to determine the endogenous FSH. If, according to the analysis results, the FSH level is 5 IU/L or less (sufficient suppression of the endogenous gonadotropin production), the volunteers can be invited to the study centre to have a subcutaneous injection of the study drug or the comparator drug made. If the FSH level appears to be higher than 5 IU/L, the volunteers will have to be excluded from the study and replaced by the back-ups. After the 28-day preparation period (including 7 days without COC and 21 days of Yarina® administration), the volunteers with the FSH level of 5 IU/L and less are to continue with Yarina®.
Examination of the volunteers at the study stage I and II	Before each drug product administration, major vital signs (BP, pulse, and body temperature) will be evaluated, physical check-up will be carried out, pregnancy test (for women of child bearing potential), respiratory alcohol level test, urine analysis for drugs and narcotic substances abuse, USI of pelvic organs; blood sampling for endogenous FSH (control point to assess

	the suppression of endogenous gonadotropins production), luteinizing hormone, and estradiol will be performed. During the whole study, major vital signs are periodically evaluated (BP, pulse, and body temperature); concomitant therapy is assessed, and the undesirable events are collected and recorded.
Control examination	The control check-up (7 days after the last injection of follitropin alfa) includes: physical check-up; 12-lead ECG recording; major vital signs evaluation (BP, pulse, and body temperature); urine analysis; complete blood count, blood biochemistry; coagulogram. During the subsequent period until day 28 of the follow-up period, the Study Doctor should ring up the volunteers to clarify the information about their well-being after 14, 21, and 28 days (i.e. every week) following the last injection of follitropin alfa.
Inclusion criteria:	1. Women aged 18 to 40 years, inclusively; available Informed Consent form signed by the volunteer to be enrolled in the study. 2. body mass index (BMI) of 18.5 to 30 kg/m^2 according to the Quetelet index, in case of a body weight of more than 45 kg; 3. According to the Investigator, the ability of the volunteer to follow the requirements set forth in the Protocol; 4. Verified "healthy" diagnosis according to the data from the medical history, as well as standard clinical, laboratory, and instrumental examination data: - absence of abnormalities of the cardiovascular, respiratory, nervous, hematological, endocrine, and gastrointestinal systems, hepatic and renal disorders in past medical history and at the time of screening examination; - results of complete blood count and blood biochemistry, coagulogram, and urine analysis during the screening examination should be within the reference values accepted at the study centre. Screening laboratory examinations should be performed not more than 7 days before the study enrollment; 5. Administration of combined oral contraceptives for at least 2 consecutive menstrual periods before the study enrollment; 6. Regular menstrual periods (with a duration of 24-35 days) that existed

	prior to the initiation of oral contraceptives. 7. Presence of both ovaries 8. Negative urine test for narcotic substances and super-potent drugs; 9. negative respiratory alcohol level test. 10. The study female participants and their sexual partners are informed and are voluntarily ready to use at least one barrier contraceptive method or a spermicide in addition to the administered contraceptive, starting from the week before the study enrollment and up to 4 weeks after the last dose of the study drug;
Non-inclusion criteria:	1. Known hypersensitivity to the active substance or to any of the excipients of the study drugs or their intolerance, as well as to the active substance or to any of the excipients of Yarina®; 2. A positive history of allergies, angioedema (congenital or idiopathic) in past medical history – the risk of rapid growth of angioedema; 3. Ovarian hyperstimulation syndrome events in past medical history (at any time before the study enrollment); 4. Impossibility to insert a venous catheter for blood sampling (for example, as a result of dermal diseases in vein puncture sites); 5. Polycystic ovarian syndrome, cystic lesions or idiopathic ovarian enlargement, menstrual disorders of any origin, female genital organ neoplasms (in particular, in past medical history), and dysplastic/neoplastic processes in the neck of the uterus (including those found during the screening examination); 6. Deep vein thrombosis, thromboembolism of the pulmonary artery (including those in past medical history). 7. Malignant neoplasms in past medical history at any time before the study entry; 8. Thyroid dysfunction; 9. Regular oral or parenteral administration of any drug products, including over-the-counter agents, vitamins, homeopathic medicines, and biologically active supplements, less than two weeks before the study enrollment (with the exception of COCs); 10. Intake or parenteral administration of any drug products, including over-the-counter agents, vitamins, homeopathic medicines, and biologically active supplements, producing expressed effects on hemodynamics, hepatic

	function, as well as of the following medicinal products: - FSH preparations - LH preparations - HCG preparations - clomifene - gonadotrophin-releasing hormone analogues; 11. Cardiovascular, bronchopulmonary, nervous, and endocrine diseases, as well as gastrointestinal, hepatic, renal, hematological, immune, and mental diseases; 12. Acute infectious diseases less than 4 weeks before the initiation of the study; 13. Systolic pressure lower than 100 mm Hg or higher than 130 mm Hg; diastolic pressure lower than 70 mm Hg or higher than 90 mm Hg; heart rate lower than 60 bpm or higher than 80 bpm; 14. Blood donation (450 mL of blood or plasma and more) less than 3 months before the initiation of the study; 15. Participation in clinical studies of drug products less than 3 months before the initiation of this study; 16. Intake of more than 5 units of alcohol per week (where each unit is equal to 50 mL of distilled spirits, 200 mL of dry wine, or 500 mL of beer) or history of alcohol addiction, drug addition, abuse of medicinal products; 17. Smoking of more than 5 cigarettes per day; 18. Positive urine analysis for drugs and narcotic substances abuse, including cocaine, cannabis, amphetamines, barbiturates, and opioids; 19. Positive respiratory alcohol level test; 20. Positive pregnancy test in women; 21. Lactation period; 22. Any reason, which according to the Investigator, may prevent participation of the volunteer in the study; 23. Congenital lactose intolerance, lactase deficiency, or glucose-galactose malabsorption (due to lactose monohydrate contained in Yarina).
Study duration:	Expected duration of participation in the study for each subject is about 73 days, including the screening period (up to 7 days), preparation period (up to 28 days), the 1st period (9 days), the 2nd period (9 days), and the follow-up period (28 days starting from the first day of the 2nd period). The wash-

	out period is 10 days.
Analytical method	Blood plasma concentrations of follitropin alfa will be determined by enzyme-linked immunosorbent assay (ELISA).
Pharmacokinetic parameters	Areas under the pharmacokinetic "concentration-time" curves (AUC_{0-t}), peak concentration (C_{max}), time to peak concentration (T_{max}), elimination half-life ($T_{1/2}$), relative absorption rate C_{max}/AUC_{0-t}
Statistical analysis:	Statistical comparison of the obtained results will comprise the calculation of parametric bilateral 90 % confidence intervals for the ratios of the corresponding mean values of the pharmacokinetic parameters of the study drug and comparator drug. The equivalence of the pharmacokinetics of the drug products will be proven if the limits of the evaluated confidence intervals for the ratios of the mean values of $AUC_{0-t,}$ C_{max} и C_{max}/ AUC_{0-t} of follitropin alpha following the administration of the study drug and comparator drug are in the range of 80-125 %.